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| NEWS | 1 | | Web Page URLs for STN Seminar Schedule - N. America |
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| NEWS | 4 | DEC 18 | CA/CAplus patent kind codes updated |
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| NEWS | 22 | FEB 26 | IFICDB/IFIPAT/IFIUDB reloaded with enhancements |
| NEWS | 23 | FEB 26 | CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases |
| NEWS | 24 | MAR 15 | WPIDS/WPIX enhanced with new FRAGHITSTR display format |
| NEWS | 25 | MAR 16 | CASREACT coverage extended |
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| NEWS | 30 | APR 02 | JICST-EPLUS removed from database clusters and STN |

NEWS EXPRESS  NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT
              MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
              AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

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| NEWS IPC8 | For general information regarding STN implementation of IPC 8 |
| NEWS X25 | X.25 communication option no longer available |

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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FILE 'MEDLINE' ENTERED AT 17:08:51 ON 16 APR 2007

FILE 'EMBASE' ENTERED AT 17:08:51 ON 16 APR 2007


FILE 'BIOSIS' ENTERED AT 17:08:51 ON 16 APR 2007


FILE 'SCISEARCH' ENTERED AT 17:08:51 ON 16 APR 2007


FILE 'CAPLUS' ENTERED AT 17:08:51 ON 16 APR 2007


=> s screening
L1     1048993 SCREENING

=> s l1 and detecting
L2       32850 L1 AND DETECTING

=> s l2 and tumor metastasis
L3          21 L2 AND TUMOR METASTASIS

=> s l3 and anti-VEGF-D
L4           0 L3 AND ANTI-VEGF-D

=> s l2 and anti-VEGF-D
L5           0 L2 AND ANTI-VEGF-D

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L6        8098 L2 AND ANTIBOD?

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L7           0 L6 AND UNPROCESSED VEGF-D

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L8           3 L6 AND VEGF-D

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PROCESSING COMPLETED FOR L8
L9            3 DUP REMOVE L8 (0 DUPLICATES REMOVED)

=> d l9 1-3 cbib abs

L9 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2003:282828 Document No. 138:298132 Modulators of VEGF or VEGFR binding to neuropilin-2, materials and methods for detecting said modulators, and therapeutic uses of the modulators.. Alitalo, Kari; Karkkainen, Marika; Karila, Kaisa (Ludwig Institute for Cancer Research, USA; Licentia Ltd.). PCT Int. Appl. WO 2003029814 A2 20030410, 181 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-EP11069 20021001. PRIORITY: US 2001-326326P 20011001.

AB The present invention relates to identifying modulators of VEGF-C binding to the nervous system transmembrane protein neuropilin-2 and materials and methods for detecting said modulators. A method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGF-C polypeptide is claimed comprising steps of: (a) contacting a neuropilin composition with a VEGF-C composition, in the presence and in the absence of a putative modulator compound; (b) detecting binding between the neuropilin polypeptide and the VEGF-C polypeptide in the presence and absence of the putative modulator compound; and (c) identifying a modulator compound based on a decrease or increase in binding in the presence of the putative modulator compound as compared to binding in the absence of the putative modulator compound The neuropilin receptor composition comprises a neuropilin receptor extracellular domain fragment bound to a solid support or a neuropilin receptor extracellular domain fragment fused to an Ig Fc fragment. The VEGF-C composition comprises a purified mammalian prepro-VEGF-C polypeptide or a fragment. A method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGFR-3 polypeptide is also claimed. The VEGFR-3 composition used in the method comprises a receptor extracellular domain fragment bound to a solid support or a receptor extracellular domain fragment fused to an Ig Fc fragment. Addnl. claimed is a method for screening for selectivity of a modulator of VEGF-C, VEGFR, or neuropilin biol. activity. A method of modulating growth, migration, or proliferation of cells, specifically neurons, in a mammalian organism by administering a composition comprising a neuropilin polypeptide or fragment, and a VEGF, a PlGF, a semaphorin, or a bispecific antibody specific for the neuropilin receptor and for a VEGF-C polypeptide or for a neuropilin receptor and a VEGFR is also claimed.

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2002:575554 Document No. 137:135068 Methods for treating neoplastic disease characterized by vascular endothelial growth factor D expression, for screening for neoplastic disease or metastatic risk, and for maintaining vascularization of tissue. Achen, Marc; Stacker, Steven (Australia). U.S. Pat. Appl. Publ. US 2002102260 A1 20020801, 45 pp., Cont.-in-part of U.S. Ser. No. 796,714. (English). CODEN: USXXCO. APPLICATION: US 2001-956095 20010920. PRIORITY: US 2000-186361P 20000302; US 2000-234196P 20000920; US 2001-796714 20010302.

AB A method for treating and alleviating disease characterized by the expression of VEGF-D involving screening to find an organism with tumor cells expressing VEGF-D and administering an effective amount of a VEGF-D antagonist; a method for screening for neoplastic disease, where detection of VEGF-D on or in a sample such as tumor cells, blood vessel endothelial cells or lymph vessel endothelial cells indicates neoplastic disease; a method for promoting and maintaining

vascularization of normal tissue in an organism involving administering a vascularization promoting amount of VEGF-D or a fragment or analog thereof to the organism; a method for screening tumors for metastatic risk involving detecting expression of VEFG-D by a tumor which indicates metastatic risk; and a method of detecting micro-metastasis of neoplastic disease involving detection of VEGF -D on or in a tissue sample which indicates metastasis of a neoplastic disease.

L9 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2001:661270 Document No. 135:205534 Methods for treating, screening for, and detecting cancers expressing vascular endothelial growth factor D (VEGF-D). Achen, Marc; Stacker, Steven (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001064235 A1 20010907, 78 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US6791 20010302. PRIORITY: US 2000-PV186361 20000302.
AB A method for treating and alleviating melanomas and various cancers characterized by the expression of VEGF-D by the tumor comprises screening to find an organism with tumor cells expressing VEGF-D and administering an effective amount of a VEGF-D antagonist to prevent binding of VEGF-D. Also provided are methods for screening for neoplastic diseases, where detection of VEGF-D on or in cells such as tumor cells, blood vessel endothelial cells, lymph vessel endothelial cells, and/or cells with potential neoplastic growth indicates neoplastic disease; a method for promoting and maintaining vascularization of normal tissue in an organism by administering VEGF-D or a fragment or analog thereof; methods for screening tumors for metastatic risk where expression of VEGF-D by the tumor indicates metastatic risk; and methods to detect micro-metastasis of neoplastic disease where detection of VEGF-D on or in a tissue sample indicates metastasis of neoplastic disease.

=> s detect?
L10 5876906 DETECT?

=> s l10 and VEGF-D
L11 285 L10 AND VEGF-D

=> s l11 and unprocessed VEGF_D
L12 5 L11 AND UNPROCESSED VEGF_D

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PROCESSING COMPLETED FOR L12
L13 1 DUP REMOVE L12 (4 DUPLICATES REMOVED)

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L13  ANSWER 1 OF 1     MEDLINE on STN                    DUPLICATE 1
2000011413.    PubMed ID: 10542248.   Biosynthesis of vascular endothelial
     growth factor-D involves proteolytic processing which generates
     non-covalent homodimers. Stacker S A; Stenvers K; Caesar C; Vitali A;
     Domagala T; Nice E; Roufail S; Simpson R J; Moritz R; Karpanen T; Alitalo
     K; Achen M G. (Ludwig Institute for Cancer Research, Royal Melbourne
     Hospital, Parkville, Victoria 3050, Australia..
     steven.stacker@ludwig.edu.au) . The Journal of biological chemistry, (1999
     Nov 5) Vol. 274, No. 45, pp. 32127-36.  Journal code: 2985121R. ISSN:
     0021-9258. Pub. country: United States. Language: English.
AB   Vascular endothelial growth factor-D (VEGF-D) binds
     and activates the endothelial cell tyrosine kinase receptors VEGF
     receptor-2 (VEGFR-2) and VEGF receptor-3 (VEGFR-3), is mitogenic for
     endothelial cells, and shares structural homology and receptor specificity
     with VEGF-C.  The primary translation product of VEGF-D
     has long N- and C-terminal polypeptide extensions in addition to a central
     VEGF homology domain (VHD).  The VHD of VEGF-D is
     sufficient to bind and activate VEGFR-2 and VEGFR-3.  Here we report that
     VEGF-D is proteolytically processed to release the VHD.
     Studies in 293EBNA cells demonstrated that VEGF-D
     undergoes N- and C-terminal cleavage events to produce numerous secreted
     polypeptides including a fully processed form of M(r) approximately 21,000
     consisting only of the VHD, which is predominantly a non-covalent dimer.
     Biosensor analysis demonstrated that the VHD has approximately 290- and
     approximately 40-fold greater affinity for VEGFR-2 and VEGFR-3,
     respectively, compared with unprocessed VEGF-D
     .  In situ hybridization demonstrated that embryonic lung is a major site
     of expression of the VEGF-D gene.  Processed forms of
     VEGF-D were detected in embryonic lung
     indicating that VEGF-D is proteolytically processed in
     vivo.


=> s (achen m?/au or stacker s?/au)
L14        529 (ACHEN M?/AU OR STACKER S?/AU)

=> s l14 and VEGF-D
L15        179 L14 AND VEGF-D

=> s l15 and anti-VEGF-D
L16          9 L15 AND ANTI-VEGF-D

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PROCESSING COMPLETED FOR L16
L17           5 DUP REMOVE L16 (4 DUPLICATES REMOVED)

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L17  ANSWER 1 OF 5  BIOSIS  COPYRIGHT (c) 2007 The Thomson Corporation  on STN
2007:12833  Document No.: PREV200700018332. Antibodies to truncated
     VEGF-D and uses thereof. Anonymous; Achen, Marc
     G. [Inventor]; Stacker, Steven Alan [Inventor]. Parkville,
     Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.:
     US 07097986 20060829. Official Gazette of the United States Patent and
     Trademark Office Patents, (AUG 29 2006)
     CODEN: OGUPE7. ISSN: 0098-1133. Language: English.
AB   The invention is based on the isolation of antibodies that were made to a
     polypeptide having the amino acid sequence for a truncated VEGF-
     D.  One of these antibodies can interfere with the activity of
     VEGF-D mediated by VEGFR-2 and interfere with the
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binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L17 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
2005:1026912 Document No. 143:304651 Chimeric and humanized anti-VEGF-D antibodies and methods of use for modulating angiogenesis and lymphangiogenesis. Achen, Marc G.; Stacker, Stephen; Renner, Christoph (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2005087177 A2 20050922, 126 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US7283 20050307. PRIORITY: US 2004-550441P 20040305.
AB The present invention relates to materials and methods for modulating angiogenesis and lymphangiogenesis. The compns. of the invention provide chimeric and/or humanized anti-VEGF-D (vascular endothelial growth factor D) antibody substances, antibodies, polypeptides and fragments thereof useful for modulating angiogenesis and lymphangiogenesis in a subject. In one aspect, the anti-VEGF-D antibody comprises complementarity determining regions (CDR) from a mouse antibody and framework regions (FR) from a non-murine (such as human) source. In another aspect, antibody regions have been altered by amino acid substitution to be more homologous to a human antibody sequence. Provided are protein and DNA sequences for VEGF-D antibody substances.

L17 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2002:334517 Document No.: PREV200200334517. Antibodies to truncated VEGF-D and thereof. Achen, Marc G. [Inventor, Reprint author]; Stacker, Steven Alan [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 6383484 20020507. Official Gazette of the United States Patent and Trademark Office Patents, (May 7, 2002) Vol. 1258, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133. Language: English.
AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated VEGF-D. One of these antibodies can interfere with the activity of VEGF-D mediated by VEGFR-2 and interfere with the binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L17 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2001:112744 Document No.: PREV200100112744. VEGF-D promotes the metastatic spread of tumor cells via the lymphatics. Stacker, Steven A. [Reprint author]; Caesar, Carol; Baldwin, Megan E.; Thornton, Gillian E.; Williams, Richard A.; Prevo, Remko; Jackson, David G.; Nishikawa, Shin-Ichi; Kubo, Hajime; Achen, Marc G.. Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Melbourne, VIC, Australia. steven.stacker@ludwig.edu.au. Nature Medicine, (February, 2001) Vol. 7, No. 2, pp. 186-191. print. ISSN: 1078-8956. Language: English.
AB Metastasis to local lymph nodes via the lymphatic vessels is a common step in the spread of solid tumors. To investigate the molecular mechanisms

underlying the spread of cancer by the lymphatics, we examined the ability of vascular endothelial growth factor (VEGF)-D, a ligand for the lymphatic growth factor receptor VEGFR-3/Flt-4, to induce formation of lymphatics in a mouse tumor model. Staining with markers specific for lymphatic endothelium demonstrated that VEGF-D induced the formation of lymphatics within tumors. Moreover, expression of VEGF-D in tumor cells led to spread of the tumor to lymph nodes, whereas expression of VEGF, an angiogenic growth factor which activates VEGFR-2 but not VEGFR-3, did not. VEGF-D also promoted tumor angiogenesis and growth. Lymphatic spread induced by VEGF-D could be blocked with an antibody specific for VEGF-D. This study demonstrates that lymphatics can be established in solid tumors and implicates VEGF family members in determining the route of metastatic spread.

L17 ANSWER 5 OF 5 MEDLINE on STN DUPLICATE 1
2000247148. PubMed ID: 10785369. Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. Achen M G; Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; Stacker S A. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . European journal of biochemistry / FEBS, (2000 May) Vol. 267, No. 9, pp. 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Vascular endothelial growth factor-D (VEGF-D), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. VEGF-D consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human VEGF-D in order to generate VEGF-D antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed VEGF-D. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature VEGF-D for binding to both VEGFR-2 and VEGFR-3 for binding to mature VEGF-D. This indicates that the binding epitopes on VEGF-D for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to VEGF-D. The anti-(VEGF-D) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of VEGF-D .

=> s l14 and antibod?
L18 139 L14 AND ANTIBOD?

=> s l18 and VEGF-D
L19 52 L18 AND VEGF-D

=> s l19 and VEGFR-2
L20 36 L19 AND VEGFR-2

=> s l20 and VEGFR-3

L21 36 L20 AND VEGFR-3

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L22 16 DUP REMOVE L21 (20 DUPLICATES REMOVED)

=> d l22 1-16 cbib abs

L22 ANSWER 1 OF 16 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2007:12833 Document No.: PREV200700018332. Antibodies to truncated VEGF-D and uses thereof. Anonymous; Achen, Marc G. [Inventor]; Stacker, Steven Alan [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 07097986 20060829. Official Gazette of the United States Patent and Trademark Office Patents, (AUG 29 2006) CODEN: OGUPE7. ISSN: 0098-1133. Language: English.
AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated VEGF-D. One of these antibodies can interfere with the activity of VEGF-D mediated by VEGFR -2 and interfere with the binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L22 ANSWER 2 OF 16 MEDLINE on STN DUPLICATE 1
2006451923. PubMed ID: 16877368. Lymphangiogenic growth factor responsiveness is modulated by postnatal lymphatic vessel maturation. Karpanen Terhi; Wirzenius Maria; Makinen Taija; Veikkola Tanja; Haisma Hidde J; Achen Marc G; Stacker Steven A; Pytowski Bronislaw; Yla-Herttuala Seppo; Alitalo Kari. (Molecular/Cancer Biology Laboratory, Biomedicum Helsinki, P.O.B. 63 (Haartmaninkatu 8), FI-00014 University of Helsinki, Finland. ) The American journal of pathology, (2006 Aug) Vol. 169, No. 2, pp. 708-18. Journal code: 0370502. ISSN: 0002-9440. Pub. country: United States. Language: English.
AB Lymphatic vessel plasticity and stability are of considerable importance when attempting to treat diseases associated with the lymphatic vasculature. Development of lymphatic vessels during embryogenesis is dependent on vascular endothelial growth factor (VEGF)-C but not VEGF-D. Using a recombinant adenovirus encoding a soluble form of their receptor VEGFR-3 (AdVEGFR-3-Ig), we studied lymphatic vessel dependency on VEGF-C and VEGF-D induced VEGFR-3 signaling in postnatal and adult mice. Transduction with AdVEGFR-3-Ig led to regression of lymphatic capillaries and medium-sized lymphatic vessels in mice under 2 weeks of age without affecting collecting lymphatic vessels or the blood vasculature. No effect was observed after this period. The lymphatic capillaries of neonatal mice also regressed partially in response to recombinant VEGFR-3-Ig or blocking antibodies against VEGFR-3, but not to adenovirus-encoded VEGFR-2-Ig. Despite sustained inhibitory VEGFR -3-Ig levels, lymphatic vessel regrowth was observed at 4 weeks of age. Interestingly, whereas transgenic expression of VEGF-C in the skin induced lymphatic hyperplasia even during embryogenesis, similar expression of VEGF-D resulted in lymphangiogenesis predominantly after birth. These results indicate considerable plasticity of lymphatic vessels during the early postnatal period but not thereafter, suggesting that anti-lymphangiogenic therapy can be safely applied in adults.

L22 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN

2005:1260640 Document No. 144:17173 Method for inhibiting angiogenesis and/or lymphangiogenesis. Mccoll, Bradley; Stacker, Steven; Achen, Marc (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2005112971 A1 20051201, 38 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US17639 20050520. PRIORITY: US 2004-572469P 20040520.

AB Proprotein convertase inhibitor has been found to dock proteolytic processing and activation of VEGF-C and VEGF-D and inhibit angiogenesis and/or lymphangiogenesis. Method and composition are disclosed for inhibiting angiogenesis and/or lymphangiogenesis, and for treating conditions associated with excessive angiogenesis, such as tumors and/or retinopathies, as well as conditions associated with lymphangiogenesis, such as the metastatic spread of malignancies, macular degeneration, inflammatory mediated diseases, rheumatoid arthritis, diabetic retinopathy and psoriasis in a patient. The inventive method and composition utilize proprotein convertase antagonist selected from the group consisting of an anti-proprotein convertase antibody, an antisense nucleic acid mol. against a polynucleotide coding for a proprotein convertase, and an siRNA for inhibiting proprotein convertase expression, as well as proprotein convertase inhibitors.

L22 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN

2005:1026969 Document No. 143:324792 Multivalent antibodies specific to growth factors of VEGF/PDGF family for diagnosis and treatment of fibrosis, inflammation, cancer and other diseases associated with aberrant angiogenesis. Eriksson, Ulf; Alitalo, Kari; Achen, Marc G.; Renner, Christoph; Stacker, Stephen; Li, Hong; Laakkonen, Pirjo (Ludwig Institute for Cancer Research, USA; Licentia Ltd.). PCT Int. Appl. WO 2005087812 A1 20050922, 152 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US7742 20050307. PRIORITY: US 2004-550511P 20040305; US 2004-586662P 20040709.

AB The present invention relates to materials and methods for modulating angiogenesis. The compns. of the invention provide antibody substances specific for two or more PDGF/VEGF family members, which are useful for modulating angiogenesis and lymphangiogenesis in a subject.

L22 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN

2005:1026912 Document No. 143:304651 Chimeric and humanized anti-VEGF-D antibodies and methods of use for modulating angiogenesis and lymphangiogenesis. Achen, Marc G.; Stacker, Stephen; Renner, Christoph (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2005087177 A2 20050922, 126 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB,

GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US7283 20050307. PRIORITY: US 2004-550441P 20040305.

AB The present invention relates to materials and methods for modulating angiogenesis and lymphangiogenesis. The compns. of the invention provide chimeric and/or humanized anti-VEGF-D (vascular endothelial growth factor D) antibody substances, antibodies, polypeptides and fragments thereof useful for modulating angiogenesis and lymphangiogenesis in a subject. In one aspect, the anti-VEGF-D antibody comprises complementarity determining regions (CDR) from a mouse antibody and framework regions (FR) from a non-murine (such as human) source. In another aspect, antibody regions have been altered by amino acid substitution to be more homologous to a human antibody sequence. Provided are protein and DNA sequences for VEGF-D antibody substances.

L22 ANSWER 6 OF 16 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2004:265559 Document No.: PREV200400271525. Antibodies to truncated VEGF-D and uses thereof. Achen, Marc G. [Inventor, Reprint Author]; Stacker, Steven Alan [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 6730489 20040504. Official Gazette of the United States Patent and Trademark Office Patents, (May 4 2004) Vol. 1282, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.

AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated VEGF-D. One of these antibodies can interfere with the activity of VEGF-D mediated by VEGFR -2 and interfere with the binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L22 ANSWER 7 OF 16 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2003224307 EMBASE VEGF-D is the strongest angiogenic and lymphangiogenic effector among VEGFs delivered into skeletal muscle via adenoviruses. Rissanen T.T.; Markkanen J.E.; Gruchala M.; Heikura T.; Puranen A.; Kettunen M.I.; Kholova I.; Kauppinen R.A.; Achen M.G. ; Stacker S.A.; Alitalo K.; Yla-Herttuala S.. Dr. S. Yla-Herttuala, Department of Biotechnology, A.I. Virtanen Institute, University of Kuopio, PO Box 1627, FIN-70211 Kuopio, Finland. Seppo.Ylaherttuala@uku.fi. Circulation Research Vol. 92, No. 10, pp. 1098-1106 30 May 2003.
Refs: 39.
ISSN: 0009-7330. CODEN: CIRUAL
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20030626. Last Updated on STN: 20030626

AB Optimal angiogenic and lymphangiogenic gene therapy requires knowledge of the best growth factors for each purpose. We studied the therapeutic potential of human vascular endothelial growth factor (VEGF) family members VEGF-A, VEGF-B, VEGF-C, and VEGF-D as well as a VEGFR-3-specific mutant (VEGF-C(156S)) using adenoviral gene transfer in rabbit hindlimb skeletal muscle. The significance of proteolytic processing of VEGF-D was explored using adenoviruses encoding either full-length or mature (ΔNΔC) VEGF-D. Adenoviruses expressing potent VEGFR-2 ligands, VEGF-A and VEGF-D(ΔNΔC), induced the strongest angiogenesis and

vascular permeability effects as assessed by capillary vessel and perfusion measurements, modified Miles assay, and MRI. The most significant feature of angiogenesis induced by both VEGF-A and VEGF-D(ΔNΔC) was a remarkable enlargement of microvessels with efficient recruitment of pericytes suggesting formation of arterioles or venules. VEGF-A also moderately increased capillary density and created glomeruloid bodies, clusters of tortuous vessels, whereas VEGF-D(ΔNΔC)-induced angiogenesis was more diffuse. Vascular smooth muscle cell proliferation occurred in regions with increased plasma protein extravasation, indicating that arteriogenesis may be promoted by VEGF-A and VEGF-D (ΔNΔC). Full-length VEGF-C and VEGF-D induced predominantly and the selective VEGFR-3 ligand VEGF-C(156S) exclusively lymphangiogenesis. Unlike angiogenesis, lymphangiogenesis was not dependent on nitric oxide. The VEGFR-1 ligand VEGF-B did not promote either angiogenesis or lymphangiogenesis. Finally, we found a positive correlation between capillary size and vascular permeability. This study compares, for the first time, angiogenesis and lymphangiogenesis induced by gene transfer of different human VEGFs, and shows that VEGF-D is the most potent member when delivered via an adenoviral vector into skeletal muscle.

L22 ANSWER 8 OF 16 MEDLINE on STN DUPLICATE 2

2003477107. PubMed ID: 14553837. Vascular endothelial growth factor-D expression in human atherosclerotic lesions. Rutanen Juha; Leppanen Pia; Tuomisto Tiina T; Rissanen Tuomas T; Hiltunen Mikko O; Vajanto Ismo; Niemi Mari; Hakkinen Tomi; Karkola Kari; Stacker Steven A; Achen Marc G; Alitalo Kari; Yla-Herttuala Seppo. (Department of Molecular Medicine, AI Virtanen Institute, University of Kuopio, PO Box 1627, FIN-70211 Kuopio, Finland. ) Cardiovascular research, (2003 Oct 1) Vol. 59, No. 4, pp. 971-9. Journal code: 0077427. ISSN: 0008-6363. Pub. country: Netherlands. Language: English.

AB OBJECTIVE: Vascular endothelial growth factor-D (VEGF-D ) is a recently characterized member of the VEGF family, but its expression in atherosclerotic lesions remains unknown. We studied the expression of VEGF-D and its receptors (VEGFR -2 and VEGFR-3) in normal and atherosclerotic human arteries, and compared that to the expression pattern of VEGF-A. METHODS: Human arterial samples (n=39) obtained from amputation operations and fast autopsies were classified according to the stage of atherosclerosis and studied by immunohistochemistry. The results were confirmed by in situ hybridization and RT-PCR. RESULTS: We found that while VEGF-A expression increased during atherogenesis, VEGF -D expression remained relatively stable only decreasing in complicated lesions. In normal arteries and in early lesions VEGF -D was mainly expressed in smooth muscle cells, whereas in complicated atherosclerotic lesions the expression was most prominent in macrophages and also colocalized with plaque neovascularization. By comparing the staining profiles of different antibodies, we found that proteolytic processing of VEGF-D was efficient in the vessel wall. VEGFR-2, but not VEGFR-3, was expressed in the vessel wall at every stage of atherosclerosis. CONCLUSIONS: Our results suggest that in large arteries VEGF-D is mainly expressed in smooth muscle cells and that it may have a role in the maintenance of vascular homeostasis. However, in complicated lesions it was also expressed in macrophages and may contribute to plaque neovascularization. The constitutive expression of VEGFR-2 in arteries suggests that it may be one of the principal mediators of the VEGF -D effects in large arteries.

L22 ANSWER 9 OF 16 BIOSIS  on STN

2002:334517 Document No.: PREV200200334517. Antibodies to truncated VEGF-D and thereof. Achen, Marc G. [Inventor, Reprint author]; Stacker, Steven Alan [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 6383484 20020507. Official Gazette of the United States Patent and Trademark Office Patents, (May 7, 2002) Vol. 1258, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133. Language: English.

AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated VEGF-D. One of these antibodies can interfere with the activity of VEGF-D mediated by VEGFR -2 and interfere with the binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L22 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN

2002:575554 Document No. 137:135068 Methods for treating neoplastic disease characterized by vascular endothelial growth factor D expression, for screening for neoplastic disease or metastatic risk, and for maintaining vascularization of tissue. Achen, Marc; Stacker, Steven (Australia). U.S. Pat. Appl. Publ. US 2002102260 A1 20020801, 45 pp., Cont.-in-part of U.S. Ser. No. 796,714. (English). CODEN: USXXCO. APPLICATION: US 2001-956095 20010920. PRIORITY: US 2000-186361P 20000302; US 2000-234196P 20000920; US 2001-796714 20010302.

AB A method for treating and alleviating disease characterized by the expression of VEGF-D involving screening to find an organism with tumor cells expressing VEGF-D and administering an effective amount of a VEGF-D antagonist; a method for screening for neoplastic disease, where detection of VEGF-D on or in a sample such as tumor cells, blood vessel endothelial cells or lymph vessel endothelial cells indicates neoplastic disease; a method for promoting and maintaining vascularization of normal tissue in an organism involving administering a vascularization promoting amount of VEGF-D or a fragment or analog thereof to the organism; a method for screening tumors for metastatic risk involving detecting expression of VEFG-D by a tumor which indicates metastatic risk; and a method of detecting micro-metastasis of neoplastic disease involving detection of VEGF-D on or in a tissue sample which indicates metastasis of a neoplastic disease.

L22 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN

2001:724562 Document No. 136:32077 Isolated lymphatic endothelial cells transduce growth, survival and migratory signals via the VEGF-C/D receptor VEGFR-3. Makinen, Taija; Veikkola, Tanja; Mustjoki, Satu; Karpanen, Terhi; Catimel, Bruno; Nice, Edouard C.; Wise, Lyn; Mercer, Andrew; Kowalski, Heinrich; Kerjaschki, Dontscho; Stacker, Steven A.; Achen, Marc G.; Alitalo, Kari (Molecular/Cancer Biology Laboratory and Ludwig Institute for Cancer Research, Haartman Institute and Helsinki University Hospital, Biomedicum Helsinki, University of Helsinki, Helsinki, FIN-00014, Finland). EMBO Journal, 20(17), 4762-4773 (English) 2001. CODEN: EMJODG. ISSN: 0261-4189. Publisher: Oxford University Press.

AB Vascular endothelial growth factor receptor-3 (VEGFR-3 /Flt4) binds two known members of the VEGF ligand family, VEGF-C and VEGF-D, and has a critical function in the remodelling of the primary capillary vasculature of midgestation embryos. Later during development, VEGFR-3 regulates the growth and maintenance of the lymphatic vessels. In the present study, the authors have isolated and cultured stable lineages of blood vascular and lymphatic

endothelial cells from human primary microvascular endothelium by using antibodies against the extracellular domain of VEGFR-3. The authors show that VEGFR-3 stimulation alone protects the lymphatic endothelial cells from serum deprivation-induced apoptosis and induces their growth and migration. At least some of these signals are transduced via a protein kinase C-dependent activation of the p42/p44 MAPK signaling cascade and via a wortmannin-sensitive induction of Akt phosphorylation. These results define the critical role of VEGF-C/VEGFR-3 signaling in the growth and survival of lymphatic endothelial cells. The culture of isolated lymphatic endothelial cells should now allow further studies of the mol. properties of these cells.

L22 ANSWER 12 OF 16 MEDLINE on STN DUPLICATE 3
2001212643. PubMed ID: 11175849. VEGF-D promotes the metastatic spread of tumor cells via the lymphatics. Stacker S A ; Caesar C; Baldwin M E; Thornton G E; Williams R A; Prevo R; Jackson D G; Nishikawa S; Kubo H; Achen M G. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia. ) Nature medicine, (2001 Feb) Vol. 7, No. 2, pp. 186-91. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Metastasis to local lymph nodes via the lymphatic vessels is a common step in the spread of solid tumors. To investigate the molecular mechanisms underlying the spread of cancer by the lymphatics, we examined the ability of vascular endothelial growth factor (VEGF)-D, a ligand for the lymphatic growth factor receptor VEGFR-3 /Flt-4, to induce formation of lymphatics in a mouse tumor model. Staining with markers specific for lymphatic endothelium demonstrated that VEGF-D induced the formation of lymphatics within tumors. Moreover, expression of VEGF-D in tumor cells led to spread of the tumor to lymph nodes, whereas expression of VEGF, an angiogenic growth factor which activates VEGFR-2 but not VEGFR-3, did not. VEGF-D also promoted tumor angiogenesis and growth. Lymphatic spread induced by VEGF-D could be blocked with an antibody specific for VEGF-D. This study demonstrates that lymphatics can be established in solid tumors and implicates VEGF family members in determining the route of metastatic spread.

L22 ANSWER 13 OF 16 MEDLINE on STN DUPLICATE 4
2001156199. PubMed ID: 11180159. Localization of vascular endothelial growth factor-D in malignant melanoma suggests a role in tumour angiogenesis. Achen M G; Williams R A; Minekus M P; Thornton G E; Stenvers K; Rogers P A; Lederman F; Roufail S; Stacker S A. (Ludwig Institute for Cancer Research, Post Office Box 2008, Royal Melbourne Hospital, Victoria 3050, Australia.. Marc.achen@ludwig.edu.au) . The Journal of pathology, (2001 Feb) Vol. 193, No. 2, pp. 147-54. Journal code: 0204634. ISSN: 0022-3417. Pub. country: England: United Kingdom. Language: English.

AB Expression of angiogenic and lymphangiogenic factors by tumours may influence the route of metastatic spread. Vascular endothelial growth factor (VEGF) is a regulator of tumour angiogenesis, but studies of the inhibition of solid tumour growth by neutralizing anti-VEGF antibodies indicated that other angiogenic factors may be involved. VEGF-D may be an alternative regulator because like VEGF it is angiogenic and it activates VEGF receptor-2 ( VEGFR-2), an endothelial cell receptor which is a key signalling molecule in tumour angiogenesis. This study reports the generation of monoclonal antibodies to the receptor-binding domain of VEGF-D and the use of these antibodies to localize VEGF-D in malignant melanoma. VEGF-D was detected in tumour cells and in

vessels adjacent to immunopositive tumour cells, but not in vessels distant from the tumours. These findings are consistent with a model in which VEGF-D, secreted by tumour cells, activates endothelial cell receptors and thereby contributes to the regulation of tumour angiogenesis and possibly lymphangiogenesis. In addition, VEGF-D was detected in the vascular smooth muscle, but not the endothelium, of vessels in adult colon. The endothelium of these vessels was negative for VEGFR-2 and VEGFR-3. As VEGF receptors can be up-regulated on endothelium in response to vessel damage and ischaemia, these findings of a specific localization of VEGF-D in smooth muscle of the blood vessels suggest that VEGF-D produced by vascular smooth muscle could play a role in vascular repair by stimulating the proliferation of endothelial cells.

L22 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
2000:441581 Document No. 133:72945 Antibodies to truncated VEGF-D and uses thereof. Achen, Marc G.; Stacker, Steven Alan (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2000037025 A2 20000629, 44 pp. DESIGNATED STATES: W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US31332 19991221. PRIORITY: US 1998-PV113254 19981221; US 1999-PV134556 19990517.

AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated VEGF-D. One of these antibodies can interfere with the activity of VEGF-D mediated by VEGFR-2 and interfere with the binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The antibodies, antibody fragments or compns. containing the antibodies are useful for diagnosis, prognosis, and therapy of VEGF-D or VEGF-C related diseases, e.g. cancer, diabetic retinopathy, psoriasis, arthropathy, fluid accumulation in the heart and/or lung.

L22 ANSWER 15 OF 16 MEDLINE on STN DUPLICATE 5
2000247148. PubMed ID: 10785369. Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. Achen M G; Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; Stacker S A. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . European journal of biochemistry / FEBS, (2000 May) Vol. 267, No. 9, pp. 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Vascular endothelial growth factor-D (VEGF-D), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. VEGF-D consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human VEGF-D in order to generate VEGF-D

antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed VEGF-D. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature VEGF-D for binding to both VEGFR-2 and VEGFR-3 for binding to mature VEGF-D. This indicates that the binding epitopes on VEGF-D for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to VEGF-D. The anti-( VEGF-D) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of VEGF-D.

L22 ANSWER 16 OF 16 MEDLINE on STN
2001021068. PubMed ID: 11023993. VEGF-C and VEGF-D expression in neuroendocrine cells and their receptor, VEGFR-3, in fenestrated blood vessels in human tissues. Partanen T A; Arola J; Saaristo A; Jussila L; Ora A; Miettinen M; Stacker S A; Achen M G; Alitalo K. (Molecular/Cancer Biology Laboratory and Department of Pathology, Haartman Institute, University of Helsinki, 00014 Helsinki, Finland. ) The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2000 Oct) Vol. 14, No. 13, pp. 2087-96. Journal code: 8804484. ISSN: 0892-6638. Pub. country: United States. Language: English.
AB Recently, vascular endothelial growth factor receptor 3 (VEGFR-3) has been shown to provide a specific marker for lymphatic endothelia in certain human tissues. In this study, we have investigated the expression of VEGFR-3 and its ligands VEGF-C and VEGF-D in fetal and adult tissues. VEGFR-3 was consistently detected in the endothelium of lymphatic vessels such as the thoracic duct, but fenestrated capillaries of several organs including the bone marrow, splenic and hepatic sinusoids, kidney glomeruli and endocrine glands also expressed this receptor. VEGF-C and VEGF-D, which bind both VEGFR-2 and VEGFR-3 were expressed in vascular smooth muscle cells. In addition, intense cytoplasmic staining for VEGF-C was observed in neuroendocrine cells such as the alpha cells of the islets of Langerhans, prolactin secreting cells of the anterior pituitary, adrenal medullary cells, and dispersed neuroendocrine cells of the gastrointestinal tract. VEGF-D was observed in the innermost zone of the adrenal cortex and in certain dispersed neuroendocrine cells. These results suggest that VEGF-C and VEGF-D have a paracrine function and perhaps a role in peptide release from secretory granules of certain neuroendocrine cells to surrounding capillaries.

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L24 ANSWER 1 OF 2 MEDLINE on STN DUPLICATE 1
2000247148. PubMed ID: 10785369. Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. Achen M G; Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T;

Alitalo K; Stacker S A. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . European journal of biochemistry / FEBS, (2000 May) Vol. 267, No. 9, pp. 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Vascular endothelial growth factor-D (VEGF-D), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. VEGF-D consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human VEGF-D in order to generate VEGF-D antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed VEGF-D. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature VEGF-D for binding to both VEGFR-2 and VEGFR-3 for binding to mature VEGF-D. This indicates that the binding epitopes on VEGF-D for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to VEGF-D. The anti-(VEGF-D) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of VEGF-D.

L24 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 2

2000011413. PubMed ID: 10542248. Biosynthesis of vascular endothelial growth factor-D involves proteolytic processing which generates non-covalent homodimers. Stacker S A; Stenvers K; Caesar C; Vitali A; Domagala T; Nice E; Roufail S; Simpson R J; Moritz R; Karpanen T; Alitalo K; Achen M G. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia.. steven.stacker@ludwig.edu.au) . The Journal of biological chemistry, (1999 Nov 5) Vol. 274, No. 45, pp. 32127-36. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor-D (VEGF-D) binds and activates the endothelial cell tyrosine kinase receptors VEGF receptor-2 (VEGFR-2) and VEGF receptor-3 (VEGFR-3), is mitogenic for endothelial cells, and shares structural homology and receptor specificity with VEGF-C. The primary translation product of VEGF-D has long N- and C-terminal polypeptide extensions in addition to a central VEGF homology domain (VHD). The VHD of VEGF-D is sufficient to bind and activate VEGFR-2 and VEGFR-3. Here we report that VEGF-D is proteolytically processed to release the VHD. Studies in 293EBNA cells demonstrated that VEGF-D undergoes N- and C-terminal cleavage events to produce numerous secreted polypeptides including a fully processed form of M(r) approximately 21,000 consisting only of the VHD, which is predominantly a non-covalent dimer. Biosensor analysis demonstrated that the VHD has approximately 290- and approximately 40-fold greater affinity for VEGFR-2 and VEGFR-3, respectively, compared with unprocessed VEGF-D. In situ hybridization demonstrated that embryonic lung is a major site of expression of the VEGF-D gene. Processed forms of VEGF-D were detected in embryonic lung indicating that VEGF-D is proteolytically processed in vivo.

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L7   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2007 ACS on STN
2002:594892   Document No. 137:150622  Cloning, tissue expression and
     therapeutic use of Flt4 (VEGFR-3) polypeptides, their polynucleotides, and
     antibodies in the diagnosis and treatment of cancer.  Alitalo,
     Kari; Aprelikova, Olga; Pajusola, Katri; Armstrong, Elina; Korhonen,
     Jaana; Kaipainen, Arja (Ludwig Institute for Cancer Research, USA).  PCT
     Int. Appl. WO 2002060950 A2 20020808, 173 pp.  DESIGNATED STATES: W:  AE,
     AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
     CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
     IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
     MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK,
     SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW; RW: AT, BE,
     BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT,
     LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR.  (English).  CODEN:
     PIXXD2.  APPLICATION: WO 2002-US1784 20020122.  PRIORITY: US 1994-340011
     19941114; US 1994-169079 19941114; US 1997-901710 19970728; US 2001-765534
     20010119.
AB   The present invention provide purified Flt4 receptor tyrosine kinase
     polypeptides and fragments thereof, polynucleotides encoding such
     polypeptides, antibodies that specifically bind such polypeptides, and
     uses thereof in the treatment and diagnosis of disease,
     specifically cancer.


=> s l3 and unprocessed VEGF-D
L8           0 L3 AND UNPROCESSED VEGF-D

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PROCESSING COMPLETED FOR L3
L9           34 DUP REMOVE L3 (0 DUPLICATES REMOVED)

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   1 FILES SEARCHED...
   4 FILES SEARCHED...
L10          1 L3 AND PD<20000302

=> d l10 cbib abs

L10  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2007 ACS on STN
2002:594892   Document No. 137:150622  Cloning, tissue expression and
     therapeutic use of Flt4 (VEGFR-3) polypeptides, their polynucleotides, and
     antibodies in the diagnosis and treatment of cancer.  Alitalo,
     Kari; Aprelikova, Olga; Pajusola, Katri; Armstrong, Elina; Korhonen,
     Jaana; Kaipainen, Arja (Ludwig Institute for Cancer Research, USA).  PCT
     Int. Appl. WO 2002060950 A2 20020808, 173 pp.  DESIGNATED STATES: W:  AE,
     AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
     CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
     IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
     MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK,
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SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US1784 20020122. PRIORITY: US 1994-340011 19941114; US 1994-169079 19941114; US 1997-901710 19970728; US 2001-765534 20010119.

AB The present invention provide purified Flt4 receptor tyrosine kinase polypeptides and fragments thereof, polynucleotides encoding such polypeptides, antibodies that specifically bind such polypeptides, and uses thereof in the treatment and diagnosis of disease, specifically cancer.

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---Logging off of STN---

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L11 0 L3 AND "FULL-LENGTH"

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Executing the logoff script...

=> LOG Y

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 38.21 | 38.42 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -1.56 | -1.56 |

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NEWS 4 JUL 28 IFICDB, IFIPAT, and IFIUDB reloaded with enhancements

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FILE 'HOME' ENTERED AT 17:13:12 ON 04 NOV 2008

=> file medline embase biosis scisearch caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'MEDLINE' ENTERED AT 17:13:32 ON 04 NOV 2008

FILE 'EMBASE' ENTERED AT 17:13:32 ON 04 NOV 2008
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FILE 'BIOSIS' ENTERED AT 17:13:32 ON 04 NOV 2008


FILE 'SCISEARCH' ENTERED AT 17:13:32 ON 04 NOV 2008


FILE 'CAPLUS' ENTERED AT 17:13:32 ON 04 NOV 2008


=> s VEGF-D
L1 1920 VEGF-D

=> s l1 and lymph node
L2 604 L1 AND LYMPH NODE

=> l2 nad metasta?
L2 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l2 and metastatic
L3 186 L2 AND METASTATIC

=> s l3 and pd<20000302
1 FILES SEARCHED...
4 FILES SEARCHED...
L4 2 L3 AND PD<20000302

=> d l4 1-2 cbib abs

L4 ANSWER 1 OF 2 MEDLINE on STN
2001039886. PubMed ID: 10873096. Expression of vascular endothelial growth factors A, B, C, and D and their relationships to lymph node status in lung adenocarcinoma. Niki T; Iba S; Tokunou M; Yamada T; Matsuno Y; Hirohashi S. (Pathology Division, National Cancer Center Research Institute, Tokyo, Japan. ) Clinical cancer research : an official journal of the American Association for Cancer Research, (2000 Jun) Vol. 6, No. 6, pp. 2431-9. Journal code: 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.
AB Vascular endothelial growth factors (VEGFs) C and D are novel members of the VEGF family that show some selectivity toward lymphatic endothelial cells. Recent studies suggest that VEGF-C may be involved in lymphangiogenesis and spread of cancer cells via lymphatic vessels. However, whether other VEGF family members play a role in lymph node metastasis is largely unknown. The aim of the present study was to explore whether expressions of VEGF-A, VEGF-B, VEGF-C, and VEGF-D are correlated with lymph node status in lung adenocarcinoma. Total RNA was isolated from 60 surgical specimens of lung adenocarcinoma with (n = 27) or without (n = 33) lymph node metastasis. The relative mRNA abundance of VEGF-A, VEGF-B, VEGF-C, and VEGF-D was measured by real-time reverse transcription-PCR analysis based on TaqMan fluorescence methodology. We found that, as single factors, expression of none of the four VEGF family members clearly correlated with the presence of lymph node metastasis. The only tendency noted was for higher VEGF-B and VEGF-C and lower VEGF-D levels in the node-positive group. However, two-way scatterplot analysis revealed that tumors with lymph node metastasis were associated with a pattern of low VEGF-D and high VEGF-A, VEGF-B,

or VEGF-C, such that the ratios of VEGF-D:VEGF-A, VEGF-D:VEGF-B, or VEGF-D:VEGF-C were significantly lower in the node-positive group. Strikingly, none of the 11 tumors with high VEGF-D levels metastasized to lymph nodes. Furthermore, a low VEGF-D:VEGF-C ratio correlated with the presence of lymphatic invasion, and six of seven tumors with a pattern of very high expression of VEGF-C and low expression of VEGF-D displayed lymph vessel invasion that extended along the bronchovascular tree beyond the main tumor. Finally, levels of VEGF-A, but not VEGF-B or VEGF-C, were higher in tumors with large nodal metastasis (> or = 1 cm) than in those with small (< 1 cm) nodal metastasis. These results support the hypothesis that two VEGF family members are involved in lymph node metastasis at two distinct steps; VEGF-C facilitates entry of cancer cells into the lymph vasculature, whereas VEGF-A promotes the growth of metastatic tumor through angiogenesis. The results also suggest that the balance between VEGF-C and VEGF-D could be important rather than the level of VEGF-C alone. Whether a low VEGF-D level plays a causative role in lymph node metastasis requires further investigation.

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

2000:445230 Document No. 133:333080 Expression of vascular endothelial growth factors A, B, C, and D and their relationships to lymph node status in lung adenocarcinoma. Niki, Toshiro; Iba, Sanae; Tokunou, Masahide; Yamada, Tesshi; Matsuno, Yoshihiro; Hirohashi, Setsuo (Pathology Division, National Cancer Center Research Institute, Tokyo, 104-0045, Japan). Clinical Cancer Research, 6(6), 2431-2439 (English) 2000. CODEN: CCREF4. ISSN: 1078-0432. Publisher: American Association for Cancer Research.

AB Vascular endothelial growth factors (VEGFs) C and D are novel members of the VEGF family that show some selectivity toward lymphatic endothelial cells. Recent studies suggest that VEGF-C may be involved in lymphangiogenesis and spread of cancer cells via lymphatic vessels. However, whether other VEGF family members play a role in lymph node metastasis is largely unknown. The aim of the present study was to explore whether expressions of VEGF-A, VEGF-B, VEGF-C, and VEGF-D are correlated with lymph node status in lung adenocarcinoma. Total RNA was isolated from 60 surgical specimens of lung adenocarcinoma with (n = 27) or without (n = 33) lymph node metastasis. The relative mRNA abundance of VEGF-A, VEGF-B, VEGF-C, and VEGF-D was measured by real-time reverse transcription-PCR anal. based on TaqMan fluorescence methodol. We found that, as single factors, expression of none of the four VEGF family members clearly correlated with the presence of lymph node metastasis. The only tendency noted was for higher VEGF-B and VEGF-C and lower VEGF-D levels in the node-pos. group. However, two-way scatter plot anal. revealed that tumors with lymph node metastasis were associated with a pattern of low VEGF-D and high VEGF-A, VEGF-B, or VEGF-C, such that the ratios of VEGF-D:VEGF-A, VEGF-D:VEGF-B, or VEGF-D:VEGF-C were significantly lower in the node-pos. group. Strikingly, none of the 11 tumors with high VEGF-D levels metastasized to lymph nodes. Furthermore, a low VEGF-D:VEGF-C ratio correlated with the presence of lymphatic invasion, and six of seven tumors with a pattern of very high expression of VEGF-C and low expression of VEGF-D displayed lymph vessel invasion that extended along the bronchovascular tree beyond the main tumor. Finally, levels of VEGF-A, but not VEGF-B or VEGF-C, were higher in tumors with large nodal metastasis (≥1 cm) than in those with small (<1 cm) nodal metastasis. These results support the hypothesis that

two VEGF family members are involved in lymph node metastasis at two distinct steps; VEGF-C facilitates entry of cancer cells into the lymph vasculature, whereas VEGF-A promotes the growth of metastatic tumor through angiogenesis. The results also suggest that the balance between VEGF-C and VEGF-D could be important rather than the level of VEGF-C alone. Whether a low VEGF-D level plays a causative role in lymph node metastasis requires further investigation.

=> s l1 and melanoma
L5 95 L1 AND MELANOMA

=> s l5 and breast ductal carcinoma
L6 0 L5 AND BREAST DUCTAL CARCINOMA

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1 FILES SEARCHED...
4 FILES SEARCHED...
L7 2 L5 AND PD<20000302

=> d l7 1-2 cbib abs

L7 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
2005:220119 Document No. 142:291350 RNA interference-mediated inhibition of vascular endothelial growth factor and vascular endothelial growth factor receptor gene expression using short interfering nucleic acids. McSwiggen, James; Beigleman, Leonid; Pavco, Pamela (Sirna Therapeutics, Inc., USA). U.S. Pat. Appl. Publ. US 20050054596 A1 20050310, 221 pp., Cont.-in-part of U.S. Ser. No. 670,011. (English). CODEN: USXXCO. APPLICATION: US 2004-764957 20040126. PRIORITY: US 2003-670011 20030923; US 2003-665255 20030916; WO 2003-US5022 20030220; US 2002-306747 20021127; US 2002-287949 20021104; US 2003-440129P 20030115; US 2002-409293P 20020909; US 2002-408378P 20020905; US 2002-406784P 20020829; US 2002-399348P 20020729; US 2002-393796P 20020703; US 2002-386782P 20020606; US 2002-363124P 20020311; US 2002-358580P 20020220; US 2001-334461P 20011130; WO 2002-US17674 20020529.
AB The present invention concerns methods and reagents useful in modulating vascular endothelial growth factor (VEGF, VEGF-A, VEGF-B, VEGF-C, VEGF-D) and/or vascular endothelial growth factor receptor (e.g., VEGFr1, VEGFr2 and/or VEGFr3) gene expression in a variety of applications, including use in therapeutic, diagnostic, target validation, and genomic discovery applications. Specifically, the invention relates to small nucleic acid mols., such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) mols. capable of mediating RNA interference (RNAi) against VEGF and/or VEGFr gene expression and/or activity. The small nucleic acid mols. are useful in the diagnosis and treatment of cancer, proliferative diseases, and any other disease or condition that responds to modulation of VEGF and/or VEGFr expression or activity.

L7 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
1999:468435 Document No. 131:83470 Expression vectors and cell lines expressing vascular endothelial growth factor D, and method of treating melanomas. Achen, Marc G.; Stacker, Steven Alan; Alitalo, Kari (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 9933485 A1 19990708, 79 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, NZ; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US27373 19981223. PRIORITY: AU 1997-1131 19971224; US 1998-87392 19980529.
AB This invention relates to expression vectors comprising VEGF-

D and its biol. active derivs., cell lines stably expressing VEGF-D and its biol. active derivs., and to a method of making a polypeptide using these expression vectors and host cells. Optionally, VEGF-D produced by the cell line of the invention is linked to an epitope tag such as FLAG, hexahistidine, or I-SPY, to facilitate purification of the polypeptide by affinity chromatog. The mammalian cell line may preferably be the 293-EBNA human embryonal kidney cell line, and several Apex-3 plasmid expression constructs are provided. The invention also relates to a method for treating and alleviating melanomas or tumors expressing VEGF-D and various diseases.

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=> s l1 and breast ductal carcinoma
L8          11 L1 AND BREAST DUCTAL CARCINOMA

=> s l8 and pd<20000302
   1 FILES SEARCHED...
   3 FILES SEARCHED...
L9           0 L8 AND PD<20000302

=> l1 and squamous cell carcinoma
L1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
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=> s l1 and squamous cell carcinoma
L10         71 L1 AND SQUAMOUS CELL CARCINOMA

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L11          7 L10 AND PD<20000302

=> d l11 1-7 cbib abs

L11  ANSWER 1 OF 7     MEDLINE on STN
2001174809.    PubMed ID: 11235991.   Vascular endothelial growth factor family
     members are differentially regulated by c-erbB signaling in head and neck
     squamous carcinoma cells. O-charoenrat P; Rhys-Evans P; Modjtahedi H;
     Eccles S A. (Department of Head and Neck Surgery, Royal Marsden Hospital,
     London, UK.. pornchai@icr.ac.uk) . Clinical & experimental metastasis,
     (2000) Vol. 18, No. 2, pp. 155-61.  Journal code: 8409970. ISSN:
     0262-0898. Pub. country: Netherlands. Language: English.
AB   Aberrant expression of tyrosine kinases such as c-erbB and EGFR
     contributes to the progression of head and neck squamous
     cell carcinomas (HNSCCs).  One mechanism may be
     potentiation of angiogenesis, since upregulation of vascular endothelial
     growth factor (VEGF) expression by activation of epidermal growth factor
     receptor (EGFR) and/or c-erbB-2 has been described.  Firstly, we
     demonstrated expression of all 4 members of the VEGF family in a panel of
     15 HNSCC cell lines which over-express one or more c-erbB receptors.  We
     then explored the regulatory roles of three major ligands with different
     selectivity of binding to c-erbB receptors (namely transforming growth
     factor-alpha (TGF-alpha), betacellulin (BTC) and heregulin-beta1
     (HRG-beta1)) on VEGF-A, B, C and D expression in selected HNSCC lines.
     Using semi-quantitative reverse transcription-PCR, we showed that all
     three c-erbB ligands up-regulated VEGF-A mRNA (all isoforms) and VEGF-C
     (BTC max at 1-10 nM; TGF-alpha and HRG-beta1 max at 10-100 nM) but had no
     effect on VEGF-B.  Interestingly, all ligands simultaneously
     down-regulated the expression of VEGF-D mRNA.  A
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monoclonal antibody (mAb) which blocks EGFR ligand binding (ICR62) down-regulated the basal levels of VEGF-A (all isoforms) and VEGF-C, had no detectable effects on VEGF-B and increased VEGF-D. ICR62 also reversed the effects of all three erbB ligands (TGF-alpha, BTC and HRG-beta1) on VEGF-A, VEGF-C and VEGF-D expression. An anti-c-erbB-2 mAb (ICR12) showed similar effects on basal or ligand-modulated expression of VEGF in these cell lines, although to a lesser extent. Our results reveal that the four VEGF genes are regulated by c-erbB signaling pathways in a strikingly different manner, suggesting that they serve distinct, although perhaps complimentary (VEGF-A and VEGF-C) or antagonistic (VEGF-D) functions. The EGFR and c-erbB-2 signaling pathway(s) plays a role in VEGF regulation in HNSCC, although EGFR would appear to be dominant in this cell type.

L11 ANSWER 2 OF 7 MEDLINE on STN

2001138019. PubMed ID: 11147670. Tumor angiogenesis. Detmar M. (Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown 02129, USA.. michael.detmar@cbrc2.mgh.harvard.edu) . The journal of investigative dermatology. Symposium proceedings / the Society for Investigative Dermatology, Inc. [and] European Society for Dermatological Research, (2000 Dec) Vol. 5, No. 1, pp. 20-3. Ref: 56. Journal code: 9609059. ISSN: 1087-0024. Pub. country: United States. Language: English.

AB In order to grow beyond minimal size and to metastasize, tumors need to induce the growth of new blood vessels (angiogenesis). Whereas in normal tissues, vascular quiescence is maintained by the dominant influence of endogenous angiogenesis inhibitors over angiogenic stimuli, tumor angiogenesis is induced by increased secretion of angiogenic factors and/or by downregulation of angiogenesis inhibitors. Recent evidence suggests vascular endothelial growth factor (VEGF) as the major tumor angiogenesis factor, promoting tumor growth, invasion, and metastasis. Conversely, blocking of VEGF function inhibits angiogenesis and suppresses tumor growth in vivo. Newly identified members of the VEGF family of angiogenesis factors include placental growth factor, VEGF-B, VEGF-C, and VEGF-D, and show overlapping binding patterns to specific endothelial cell receptors. VEGF-C appears to play a major role as a lymphangiogenesis factor and as a growth factor for Kaposi's sarcoma. In contrast, endogenous inhibitors prevent blood vessel growth in normal tissues. In particular, thrombospondin-1 (TSP-1) and TSP-2 are expressed in normal skin and, when introduced into squamous cell carcinomas, potently inhibit malignant tumor growth via inhibition of tumor angiogenesis.

L11 ANSWER 3 OF 7 EMBASE 

2001017946 EMBASE Tumor angiogenesis.

Detmar, M., Dr. (correspondence). CBRC/Department of Dermatology, Massachusetts General Hospital, Building 149, 13th Street, Charlestown, MA 02129, United States. michael.detmar@cbrc2.mgh.harvard.edu.

Journal of Investigative Dermatology Symposium Proceedings Vol. 5, No. 1, pp. 20-23 2000.

Refs: 56.

ISSN: 1087-0024. CODEN: JDSPFO.

Pub. Country: United States. Language: English. Summary Language: English.

Entered STN: 20010201. Last Updated on STN: 20010201

AB In order to grow beyond minimal size and to metastasize, tumors need to induce the growth of new blood vessels (angiogenesis). Whereas in normal tissues, vascular quiescence is maintained by the dominant influence of endogenous angiogenesis inhibitors over angiogenic stimuli, tumor angiogenesis is induced by increased secretion of angiogenic factors and/or by downregulatlon of angiogenesis inhibitors. Recent evidence suggests vascular endothelial growth factor (VEGF) as the major tumor

angiogenesis factor, promoting tumor growth, invasion, and metastasis. Conversely, blocking of VEGF function inhibits angiogenesis and suppresses tumor growth in vivo. Newly identified members of the VEGF family of angiogenesis factors include placental growth factor, VEGF-B, VEGF-C, and VEGF-D, and show overlapping binding patterns to specific endothelial cell receptors. VEGF-C appears to play a major role as a lymphangiogenesis factor and as a growth factor for Kaposi's sarcoma. In contrast, endogenous inhibitors prevent blood vessel growth in normal tissues. In particular, thrombospondin-1 (TSP-1) and TSP-2 are expressed in normal skin and, when introduced into squamous cell carcinomas, potently inhibit malignant tumor growth via inhibition of tumor angiogenesis.

L11 ANSWER 4 OF 7 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
2001:150850 Document No.: PREV200100150850. Vascular endothelial growth factor family members are differentially regulated by c-erbB signaling in head and neck squamous carcinoma cells. O-charoenrat, Pornchai [Reprint author]; Rhys-Evans, Peter; Modjtahedi, Helmout; Eccles, Suzanne A.. McElwain Laboratories, Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey, SM2 5NG, UK. pornchai@icr.ac.uk. Clinical and Experimental Metastasis, (2000) Vol. 18, No. 2, pp. 155-161. print.
CODEN: CEXMD2. ISSN: 0262-0898. Language: English.
AB Aberrant expression of tyrosine kinases such as c-erbB and EGFR contributes to the progression of head and neck squamous cell carcinomas (HNSCCs). One mechanism may be potentiation of angiogenesis, since upregulation of vascular endothelial growth factor (VEGF) expression by activation of epidermal growth factor receptor (EGFR) and/or c-erbB-2 has been described. Firstly, we demonstrated expression of all 4 members of the VEGF family in a panel of 15 HNSCC cell lines which over-express one or more c-erbB receptors. We then explored the regulatory roles of three major ligands with different selectivity of binding to c-erbB receptors (namely transforming growth factor-alpha (TGF-alpha), betacellulin (BTC) and heregulin-beta1 (HRG-beta1)) on VEGF-A, B, C and D expression in selected HNSCC lines. Using semi-quantitative reverse transcription-PCR, we showed that all three c-erbB ligands up-regulated VEGF-A mRNA (all isoforms) and VEGF-C (BTC max at 1-10 nM; TGF-alpha and HRG-beta1 max at 10-100 nM) but had no effect on VEGF-B. Interestingly, all ligands simultaneously down-regulated the expression of VEGF-D mRNA. A monoclonal antibody (mAb) which blocks EGFR ligand binding (ICR62) down-regulated the basal levels of VEGF-A (all isoforms) and VEGF-C, had no detectable effects on VEGF-B and increased VEGF-D. ICR62 also reversed the effects of all three erbB ligands (TGF-alpha, BTC and HRG-beta1) on VEGF-A, VEGF-C and VEGF-D expression. An anti-c-erbB-2 mAb (ICR12) showed similar effects on basal or ligand-modulated expression of VEGF in these cell lines, although to a lesser extent. Our results reveal that the four VEGF genes are regulated by c-erbB signaling pathways in a strikingly different manner, suggesting that they serve distinct, although perhaps complimentary (VEGF-A and VEGF-C) or antagonistic (VEGF-D) functions. The EGFR and c-erbB-2 signaling pathway(s) plays a role in VEGF regulation in HNSCC, although EGFR would appear to be dominant in this cell type.

L11 ANSWER 5 OF 7 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN
2001:116290 The Genuine Article (R) Number: 396DD. Vascular endothelial growth factor family members are differentially regulated by c-erbB signaling in head and neck squamous carcinoma cells. O-charoenrat P (Reprint); Rhys-Evans P; Modjtahedi H; Eccles S A. Inst Canc Res, McElwain Labs, Sect Canc Therapeut, Tumor Biol & Metastasis Grp, 15 Cotswold Rd, Sutton SM2 5NG, Surrey, England (Reprint); Inst Canc Res, McElwain Labs, Sect Canc Therapeut, Tumor Biol & Metastasis Grp, Sutton SM2 5NG, Surrey,

England; Royal Marsden Hosp, Dept Head & Neck Surg, London SW3 6JJ, England; Univ Surrey, European Inst Hlth & Med Sci, Guildford GU2 5XH, Surrey, England. CLINICAL & EXPERIMENTAL METASTASIS (2000) Vol. 18, No. 2, pp. 155-161. ISSN: 0262-0898. Publisher: KLUWER ACADEMIC PUBL, VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Aberrant expression of tyrosine kinases such as c-erbB and EGFR contributes to the progression of head and neck squamous cell carcinomas (HNSCCs). One mechanism may be potentiation of angiogenesis, since upregulation of vascular endothelial growth factor (VEGF) expression by activation of epidermal growth factor receptor (EGFR) and/or c-erbB-2 has been described. Firstly, we demonstrated expression of all 4 members of the VEGF family in a panel of 15 HNSCC cell lines which over-express one or more c-erbB receptors. We then explored the regulatory roles of three major ligands with different selectivity of binding to c-erbB receptors (namely transforming growth factor-alpha (TGF-alpha), betacellulin (BTC) and heregulin-beta1 (HRG-beta1)) on VEGF-A, B, C and D expression in selected HNSCC lines. Using semi-quantitative reverse transcription-PCR, we showed that all three c-erbB ligands up-regulated VEGF-A mRNA (all isoforms) and VEGF-C (BTC max at 1-10 nM; TGF-alpha and HRG-beta1 max at 10-100 nM) but had no effect on VEGF-B. Interestingly, all ligands simultaneously down-regulated the expression of VEGF-D mRNA. A monoclonal antibody (mAb) which blocks EGFR ligand binding (ICR62) down-regulated the basal levels of VEGF-A (all isoforms) and VEGF-C, had no detectable effects on VEGF-B and increased VEGF-D. ICR62 also reversed the effects of all three erbB ligands (TGF-alpha, BTC and HRG-beta1) on VEGF-A, VEGF-C and VEGF-D expression. An anti-c-erbB-2 mAb (ICR12) showed similar effects on basal or ligand-modulated expression of VEGF in these cell lines, although to a lesser extent. Our results reveal that the four VEGF genes are regulated by c-erbB signaling pathways in a strikingly different manner, suggesting that they serve distinct, although perhaps complimentary (VEGF-A and VEGF-C) or antagonistic (VEGF-D) functions. The EGFR and c-erbB-2 signaling pathway(s) plays a role in VEGF regulation in HNSCC, although EGFR would appear to be dominant in this cell type.

L11 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

2001:193609 Document No. 135:150743 Vascular endothelial growth factor family members are differentially regulated by c-erbB signaling in head and neck squamous carcinoma cells. O-Charoenrat, Pornchai; Rhys-Evans, Peter; Modjtahedi, Helmout; Eccles, Suzanne A. (Department of Head and Neck Surgery, Royal Marsden Hospital, London, SW3 6JJ, UK). Clinical & Experimental Metastasis, 18(2), 155-161 (English) 2000. CODEN: CEXMD2. ISSN: 0262-0898. Publisher: Kluwer Academic Publishers.

AB Aberrant expression of Tyr kinases such as c-erbB and EGFR contributes to the progression of head and neck squamous cell carcinomas (HNSCCs). One mechanism may be potentiation of angiogenesis, since upregulation of vascular endothelial growth factor (VEGF) expression by activation of epidermal growth factor receptor (EGFR) and/or c-erbB-2 was described. Firstly, the authors demonstrated expression of all 4 members of the VEGF family in a panel of 15 HNSCC cell lines which over-express one or more c-erbB receptors. The authors then explored the regulatory roles of 3 major ligands with different selectivity of binding to c-erbB receptors (namely transforming growth factor-α TGF-α), betacellulin (BTC) and heregulin-β1 (HRG-β1) on VEGF-A,B,C and D expression in selected HNSCC lines. Using semi-quant. reverse transcription-PCR, the authors showed that all 3 c-erbB ligands up-regulated VEGF-A mRNA (all isoforms) and VEGF-C (BTC max at 1-10 nM; TGF-α and HRG-β1 max at 10-100 nM) but had no effect on VEGF-B. Interestingly, all ligands simultaneously down-regulated the expression of VEGF-D mRNA. A

monoclonal antibody (mAb) which blocks EGFR ligand binding (ICR62) down-regulated the basal levels of VEGF-A (all isoforms) and VEGF-C, had no detectable effects on VEGF-B and increased VEGF-D. ICR62 also reversed the effects of all 3 erbB ligands (TGF-α, BTC and HRG-β1) on VEGF-A, VEGF-C and VEGF-D expression. An anti-c-erbB-2 mAb (ICR12) showed similar effects on basal or ligand-modulated expression of VEGF in these cell lines, although to a lesser extent. These results reveal that the 4 VEGF genes are regulated by c-erbB signaling pathways in a strikingly different manner, suggesting that they serve distinct, although perhaps complimentary (VEGF-A and VEGF-C) or antagonistic (VEGF-D) functions. The EGFR and c-erbB-2 signaling pathway(s) plays a role in VEGF regulation in HNSCC, although EGFR would appear to be dominant in this cell type.

L11 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
2001:103675 Document No. 135:44234 Tumor angiogenesis. Detmar, Michael (Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, 02129, USA). Journal of Investigative Dermatology Symposium Proceedings, 5(1), 20-23 (English) 2000. CODEN: JDSPFO. ISSN: 1087-0024. Publisher: Blackwell Science, Inc..
AB A review with 56 refs. To grow beyond minimal size and to metastasize, tumors need to induce the growth of new blood vessels (angiogenesis). Whereas in normal tissues, vascular quiescence is maintained by the dominant influence of endogenous angiogenesis inhibitors over angiogenic stimuli, tumor angiogenesis is induced by increased secretion of angiogenic factors and/or by downregulation of angiogenesis inhibitors. Recent evidence suggests vascular endothelial growth factor (VEGF) as the major tumor angiogenesis factor, promoting tumor growth, invasion, and metastasis. Conversely, blocking of VEGF function inhibits angiogenesis and suppresses tumor growth in vivo. Newly identified members of the VEGF family of angiogenesis factors include placental growth factor, VEGF-B, VEGF-C, and VEGF-D, and show overlapping binding patterns to specific endothelial cell receptors. VEGF-C appears to play a major role as a lymphangiogenesis factor and as a growth factor for Kaposi's sarcoma. In contrast, endogenous inhibitors prevent blood vessel growth in normal tissues. In particular, thrombospondin-1 (TSP-1) and TSP-2 are expressed in normal skin and, when introduced into squamous cell carcinomas, potently inhibit malignant tumor growth via inhibition of tumor angiogenesis.

=> s l1 and prostate cancer
L12 42 L1 AND PROSTATE CANCER

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L13 7 L2 AND PD<20000302

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L13 ANSWER 1 OF 7 MEDLINE on STN
2001039886. PubMed ID: 10873096. Expression of vascular endothelial growth factors A, B, C, and D and their relationships to lymph node status in lung adenocarcinoma. Niki T; Iba S; Tokunou M; Yamada T; Matsuno Y; Hirohashi S. (Pathology Division, National Cancer Center Research Institute, Tokyo, Japan. ) Clinical cancer research : an official journal of the American Association for Cancer Research, (2000 Jun) Vol. 6, No. 6, pp. 2431-9. Journal code: 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.
AB Vascular endothelial growth factors (VEGFs) C and D are novel members of

the VEGF family that show some selectivity toward lymphatic endothelial cells. Recent studies suggest that VEGF-C may be involved in lymphangiogenesis and spread of cancer cells via lymphatic vessels. However, whether other VEGF family members play a role in lymph node metastasis is largely unknown. The aim of the present study was to explore whether expressions of VEGF-A, VEGF-B, VEGF-C, and VEGF-D are correlated with lymph node status in lung adenocarcinoma. Total RNA was isolated from 60 surgical specimens of lung adenocarcinoma with (n = 27) or without (n = 33) lymph node metastasis. The relative mRNA abundance of VEGF-A, VEGF-B, VEGF-C, and VEGF-D was measured by real-time reverse transcription-PCR analysis based on TaqMan fluorescence methodology. We found that, as single factors, expression of none of the four VEGF family members clearly correlated with the presence of lymph node metastasis. The only tendency noted was for higher VEGF-B and VEGF-C and lower VEGF-D levels in the node-positive group. However, two-way scatterplot analysis revealed that tumors with lymph node metastasis were associated with a pattern of low VEGF-D and high VEGF-A, VEGF-B, or VEGF-C, such that the ratios of VEGF-D:VEGF-A, VEGF-D:VEGF-B, or VEGF-D:VEGF-C were significantly lower in the node-positive group. Strikingly, none of the 11 tumors with high VEGF-D levels metastasized to lymph nodes. Furthermore, a low VEGF-D:VEGF-C ratio correlated with the presence of lymphatic invasion, and six of seven tumors with a pattern of very high expression of VEGF-C and low expression of VEGF-D displayed lymph vessel invasion that extended along the bronchovascular tree beyond the main tumor. Finally, levels of VEGF-A, but not VEGF-B or VEGF-C, were higher in tumors with large nodal metastasis (> or = 1 cm) than in those with small (< 1 cm) nodal metastasis. These results support the hypothesis that two VEGF family members are involved in lymph node metastasis at two distinct steps; VEGF-C facilitates entry of cancer cells into the lymph vasculature, whereas VEGF-A promotes the growth of metastatic tumor through angiogenesis. The results also suggest that the balance between VEGF-C and VEGF-D could be important rather than the level of VEGF-C alone. Whether a low VEGF-D level plays a causative role in lymph node metastasis requires further investigation.



1999370908 EMBASE Expression of vascular endothelial growth factor (VEGF) family members in breast cancer.

Kurebayashi, Junichi (correspondence); Kunisue, Hironori; Tanaka, Katsuhiko; Yamamoto, Shigeru; Sonoo, Hiroshi. Dept. of Breast and Thyroid Surgery, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan. kure@med.kawasaki-m.ac.jp. Otsuki, Takemi. Department of Hygiene, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan. Mikami, Yoshinori. Department of Pathology, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan. Kurebayashi, Junichi (correspondence). Department of Breast Thyroid Surgery, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan. kure@med.kawasaki-m.ac.jp.

Japanese Journal of Cancer Research Vol. 90, No. 9, pp. 977-981 Sep 1999.
Refs: 17.
ISSN: 0910-5050. CODEN: JJCREP.
Pub. Country: Japan. Language: English. Summary Language: English.
Entered STN: 19991112. Last Updated on STN: 19991112

AB Vascular endothelial growth factor (VEGF)-A is known to play an important role in tumor angiogenesis. Three additional members of the VEGF family,

VEGF-B, -C and -D, have recently been discovered. VEGF-C and VEGF -D are ligands for VEGF receptor-3, which is expressed in the endothelium of lymphatic vessels. The expression of VEGF-C is known to be associated with the development of lymphatic vessels. Therefore, it is conceivable that VEGF-C and VEGF-D might play a role in the development of lymphatic vessels in solid tumors. To obtain some clue as to this role, we developed a semi-quantitative reverse transcription-polymerase chain reaction method to investigate the mRNA expression levels of each VEGF family member in breast cancer All the VEGF family members were expressed at different levels in seven human breast cancer cell lines explored. Although VEGF-A and VEGF-B expressions were detected in both node-positive and node-negative breast tumors, VEGF-C expression was detected only in node-positive tumors. VEGF-D expression was detected only in an inflammatory breast cancer and a tumor which developed an inflammatory skin metastasis. These findings suggest a possible relationship between the expression level of VEGF-C and/or VEGF-D and the development of lymphatic tumor spread.

L13 ANSWER 3 OF 7 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN

2001:61964 The Genuine Article (R) Number: 390XC. Vascular permeability factor/vascular endothelial growth factor (VPF/VEGF). Stiver S I (Reprint); Dvorak H F. JOURNAL OF CLINICAL LIGAND ASSAY (FAL 2000***) Vol. 23, No. 3, pp. 193-205. ISSN: 1081-1672. Publisher: CLINICAL LIGAND ASSAY SOC, 3139 S WAYNE RD, WAYNE, MI 48184 USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Current enthusiasm for the therapeutic application of angiogenesis to a wide range of disease processes derives in large part from studies of one of the most potent and biologically important growth factors, vascular permeability factor/vascular endothelial growth factor (VPF/VEGF). VPF/VEGF, also known as VEGF-A, is the foremost member of a large family of growth factors, which includes VEGF-B, VEGF-C, ***VEGF-D ,VEGF-E, and placenta growth factor (PIGF). VPF/VEGF acts as a key regulator in the angiogenic process by inducing hyperpermeability, proliferation, and migration of endothelial cells. More recently, VPF/VEGF has become recognized for its important role in promoting endothelial cell survival. The biological actions of VPF/VEGF are mediated through two tyrosine kinase receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1), selectively expressed on vascular endothelium, together with a recently discovered receptor, neuropilin. Expression of VPF/VEGF and its receptors is regulated primarily by hypoxia, other cytokines, oncogenes, and tumor suppressor genes. The signaling mechanisms of endothelial cell proliferation, migration, and hyperpermeability and the role of the anti-apoptotic AKT pathway in endothelial survival are areas of active research.

Angiogenesis mediated through VPF/VEGF is pivotal to the pathological entities of wound healing, ischemia, and tumor growth. Methods of detection and quantitation of VPF/VEGF in tissues and body fluids have become increasingly important as VPF/VEGF gains clinical importance in the diagnosis and treatment of disease.

L13 ANSWER 4 OF 7 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN

1999:777295 The Genuine Article (R) Number: 245PJ. Expression of vascular endothelial growth factor (VEGF) family members in breast cancer. Kurebayashi J (Reprint); Otsuki T; Kunisue H; Mikami Y; Tanaka K; Yamamoto S; Sonoo H. Kawasaki Med Sch, Dept Breast & Thyroid Surg, 577 Matsushima, Kurashiki, Okayama 7010192, Japan (Reprint); Kawasaki Med Sch, Dept Breast & Thyroid Surg, Kurashiki, Okayama 7010192, Japan; Kawasaki Med Sch, Dept Pathol, Kurashiki, Okayama 7010192, Japan. JAPANESE JOURNAL OF CANCER RESEARCH (SEP 1999) Vol. 90, No. 9, pp. 977-981. ISSN: 0910-5050

. Publisher: BUSINESS CENTER ACADEMIC SOCIETIES JAPAN, 5-16-9 HONKOMAGOME, BUNKYO-KU, TOKYO, 113-8633, JAPAN. Language: English.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Vascular endothelial growth factor (VEGF)-A is known to play an important role in tumor angiogenesis. Three additional members of the VEGF family, VEGF-B, -C and -D, have recently been discovered. VEGF-C and VEGF-D are ligands for VEGF receptor-3, which is expressed in the endothelium of lymphatic vessels. The expression of VEGF-C is known to be associated with the development of lymphatic vessels. Therefore, it is conceivable that VEGF-C: and VEGF-D might play a role in the development of lymphatic vessels in solid tumors. To obtain some clue as to this role, we developed a semi-quantitative reverse transcription-polymerase chain reaction method to investigate the mRNA expression levels of each VEGF family member in breast cancer. All the VEGF family members were expressed at different levels in seven human breast cancer cell lines explored. Although VEGF-A and VEGF-B expressions were detected in both node-positive and node-negative breast tumors, VEGF-C expression was detected only in node-positive tumors. VEGF-D expression was detected only in an inflammatory breast cancer and a tumor which developed an inflammatory skin metastasis. These findings suggest a possible relationship between the expression level of VEGF-C and/or VEGF-D and the development of lymphatic tumor spread.

L13 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

2002:594892 Document No. 137:150622 Cloning, tissue expression and therapeutic use of Flt4 (VEGFR-3) polypeptides, their polynucleotides, and antibodies in the diagnosis and treatment of cancer. Alitalo, Kari; Aprelikova, Olga; Pajusola, Katri; Armstrong, Elina; Korhonen, Jaana; Kaipainen, Arja (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2002060950 A2 20020808, 173 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US1784 20020122. PRIORITY: US 1994-340011 19941114; US 1994-169079 19941114; US 1997-901710 19970728; US 2001-765534 20010119.

AB The present invention provide purified Flt4 receptor tyrosine kinase polypeptides and fragments thereof, polynucleotides encoding such polypeptides, antibodies that specifically bind such polypeptides, and uses thereof in the treatment and diagnosis of disease, specifically cancer.

L13 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

2000:445230 Document No. 133:333080 Expression of vascular endothelial growth factors A, B, C, and D and their relationships to lymph node status in lung adenocarcinoma. Niki, Toshiro; Iba, Sanae; Tokunou, Masahide; Yamada, Tesshi; Matsuno, Yoshihiro; Hirohashi, Setsuo (Pathology Division, National Cancer Center Research Institute, Tokyo, 104-0045, Japan). Clinical Cancer Research, 6(6), 2431-2439 (English) 2000. CODEN: CCREF4. ISSN: 1078-0432. Publisher: American Association for Cancer Research.

AB Vascular endothelial growth factors (VEGFs) C and D are novel members of the VEGF family that show some selectivity toward lymphatic endothelial cells. Recent studies suggest that VEGF-C may be involved in lymphangiogenesis and spread of cancer cells via lymphatic vessels. However, whether other VEGF family members play a role in lymph node metastasis is largely unknown. The aim of the present study was to explore whether expressions of VEGF-A, VEGF-B, VEGF-C, and

VEGF-D are correlated with lymph node status in lung adenocarcinoma. Total RNA was isolated from 60 surgical specimens of lung adenocarcinoma with (n = 27) or without (n = 33) lymph node metastasis. The relative mRNA abundance of VEGF-A, VEGF-B, VEGF-C, and VEGF-D was measured by real-time reverse transcription-PCR anal. based on TaqMan fluorescence methodol. We found that, as single factors, expression of none of the four VEGF family members clearly correlated with the presence of lymph node metastasis. The only tendency noted was for higher VEGF-B and VEGF-C and lower VEGF-D levels in the node-pos. group. However, two-way scatter plot anal. revealed that tumors with lymph node metastasis were associated with a pattern of low VEGF-D and high VEGF-A, VEGF-B, or VEGF-C, such that the ratios of VEGF-D:VEGF-A, VEGF-D:VEGF-B, or VEGF-D:VEGF-C were significantly lower in the node-pos. group. Strikingly, none of the 11 tumors with high VEGF-D levels metastasized to lymph nodes. Furthermore, a low VEGF-D:VEGF-C ratio correlated with the presence of lymphatic invasion, and six of seven tumors with a pattern of very high expression of VEGF-C and low expression of VEGF-D displayed lymph vessel invasion that extended along the bronchovascular tree beyond the main tumor. Finally, levels of VEGF-A, but not VEGF-B or VEGF-C, were higher in tumors with large nodal metastasis (≥1 cm) than in those with small (<1 cm) nodal metastasis. These results support the hypothesis that two VEGF family members are involved in lymph node metastasis at two distinct steps; VEGF-C facilitates entry of cancer cells into the lymph vasculature, whereas VEGF-A promotes the growth of metastatic tumor through angiogenesis. The results also suggest that the balance between VEGF-C and VEGF-D could be important rather than the level of VEGF-C alone. Whether a low VEGF-D level plays a causative role in lymph node metastasis requires further investigation.

L13 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

1998:237244 Document No. 129:3742 Original Reference No. 129:931a,934a

Proinflammatory cytokines regulate expression of the lymphatic endothelial mitogen vascular endothelial growth factor-C. Ristimaki, Ari; Narko, Kirsi; Enholm, Berndt; Joukov, Vladimir; Alitalo, Kari (Department Bacteriology Immunology, Haartman Institute, Haartmaninkatu, FIN-00290, Finland). Journal of Biological Chemistry, 273(14), 8413-8418 (English) 1998. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB Vascular endothelial growth factor (VEGF) is a prime regulator of normal and pathol. angiogenesis. Three related endothelial cell growth factors, VEGF-B, VEGF-C, and VEGF-D were recently cloned. We have here studied the regulation of VEGF-C, a lymphatic endothelial growth factor, by angiogenic proinflammatory cytokines. Interleukin (IL)-1β induced a concentration- and a time-dependent increase in VEGF-C, but not in VEGF-B, mRNA steady-state levels in human lung fibroblasts. The increase in VEGF-C mRNA levels was mainly due to increased transcription rather than elevated mRNA stability as detected by the nuclear run-on method and by following mRNA decay in the presence of an inhibitor of transcription, resp. In contrast, angiopoietin-1 mRNA, encoding the ligand for the endothelial-specific Tek/Tie-2 receptor, was down-regulated by IL-1β. Tumor necrosis factor-α and IL-1α also elevated VEGF-C mRNA steady-state levels, whereas the IL-1 receptor antagonist and dexamethasone inhibited the effect of IL-1β. Expts. with cycloheximide indicated that the effect of IL-1β was independent of protein synthesis. Hypoxia, which is an important inducer of VEGF expression, had no effect on VEGF-B or VEGF-C mRNA levels. IL-1β and tumor necrosis factor-a also stimulated the production of VEGF-C protein by

the fibroblasts. Cytokines and growth factors have previously been shown to down-regulate VEGF receptors in vascular endothelial cells. We found that the mRNA for the VEGF- and VEGF-C-binding VEGFR-2 (KDR/Flk-1) was stimulated by IL-1β in human umbilical vein endothelial cells, whereas the mRNA levels of VEGFR-1 (Flt-1) and VEGFR-3 (Flt-4) were not altered. Our data suggest that in addition to VEGF, VEGF-C may also serve as an endothelial stimulus at sites of cytokine activation. In particular, these results raise the possibility that certain proinflammatory cytokines regulate the lymphatic vessels indirectly via VEGF-C.

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L18  ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2008 ACS on STN
2002:594892   Document No. 137:150622  Cloning, tissue expression and
     therapeutic use of Flt4 (VEGFR-3) polypeptides, their polynucleotides, and
     antibodies in the diagnosis and treatment of cancer.  Alitalo, Kari;
     Aprelikova, Olga; Pajusola, Katri; Armstrong, Elina; Korhonen, Jaana;
     Kaipainen, Arja (Ludwig Institute for Cancer Research, USA).  PCT Int.
     Appl. WO 2002060950 A2 20020808, 173 pp.  DESIGNATED STATES: W:  AE, AG,
     AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ,
     DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,
     IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
     MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
     TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW; RW: AT, BE, BF,
     BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU,
     MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR.  (English).  CODEN: PIXXD2.
     APPLICATION: WO 2002-US1784 20020122.  PRIORITY: US 1994-340011 19941114;
     US 1994-169079 19941114; US 1997-901710 19970728; US 2001-765534 20010119.
AB   The present invention provide purified Flt4 receptor tyrosine kinase
     polypeptides and fragments thereof, polynucleotides encoding such
     polypeptides, antibodies that specifically bind such polypeptides, and
     uses thereof in the treatment and diagnosis of disease, specifically
     cancer.

L18  ANSWER 2 OF 9     MEDLINE on STN                    DUPLICATE 1
2001078161.    PubMed ID: 11114740.   Vascular endothelial growth factor
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receptors in the regulation of angiogenesis and lymphangiogenesis. Karkkainen M J; Petrova T V. (Molecular Cancer Biology Laboratory, and the Ludwig Institute for Cancer Research, Haartman Institute, University of Helsinki, 00014 Helsinki, Finland. ) Oncogene, (2000 Nov 20) Vol. 19, No. 49, pp. 5598-605. Ref: 92. Journal code: 8711562. ISSN: 0950-9232. Pub. country: ENGLAND: United Kingdom. Language: English.

AB VEGFR-1 (Flt-1), VEGFR-2 (KDR) and VEGFR-3 (Flt4) are endothelial specific receptor tyrosine kinases, regulated by members of the vascular endothelial growth factor family. VEGFRs are indispensable for embryonic vascular development, and are involved in the regulation of many aspects of physiological and pathological angiogenesis. VEGF-C and VEGF -D, as ligands for VEGFR-3 are also capable of stimulating lymphangiogenesis and at least VEGF-C can enhance lymphatic metastasis. Recent studies have shown that missense mutations within the VEGFR-3 tyrosine kinase domain are associated with human hereditary lymphedema, suggesting an important role for this receptor in the development of the lymphatic vasculature.

L18 ANSWER 3 OF 9 MEDLINE on STN DUPLICATE 2

2001039886. PubMed ID: 10873096. Expression of vascular endothelial growth factors A, B, C, and D and their relationships to lymph node status in lung adenocarcinoma. Niki T; Iba S; Tokunou M; Yamada T; Matsuno Y; Hirohashi S. (Pathology Division, National Cancer Center Research Institute, Tokyo, Japan. ) Clinical cancer research : an official journal of the American Association for Cancer Research, (2000 Jun) Vol. 6, No. 6, pp. 2431-9. Journal code: 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.

AB Vascular endothelial growth factors (VEGFs) C and D are novel members of the VEGF family that show some selectivity toward lymphatic endothelial cells. Recent studies suggest that VEGF-C may be involved in lymphangiogenesis and spread of cancer cells via lymphatic vessels. However, whether other VEGF family members play a role in lymph node metastasis is largely unknown. The aim of the present study was to explore whether expressions of VEGF-A, VEGF-B, VEGF-C, and VEGF -D are correlated with lymph node status in lung adenocarcinoma. Total RNA was isolated from 60 surgical specimens of lung adenocarcinoma with (n = 27) or without (n = 33) lymph node metastasis. The relative mRNA abundance of VEGF-A, VEGF-B, VEGF-C, and VEGF-D was measured by real-time reverse transcription-PCR analysis based on TaqMan fluorescence methodology. We found that, as single factors, expression of none of the four VEGF family members clearly correlated with the presence of lymph node metastasis. The only tendency noted was for higher VEGF-B and VEGF-C and lower VEGF-D levels in the node-positive group. However, two-way scatterplot analysis revealed that tumors with lymph node metastasis were associated with a pattern of low VEGF-D and high VEGF-A, VEGF-B, or VEGF-C, such that the ratios of VEGF-D:VEGF-A, VEGF-D:VEGF-B, or VEGF-D:VEGF-C were significantly lower in the node-positive group. Strikingly, none of the 11 tumors with high VEGF-D levels metastasized to lymph nodes. Furthermore, a low VEGF-D:VEGF-C ratio correlated with the presence of lymphatic invasion, and six of seven tumors with a pattern of very high expression of VEGF-C and low expression of VEGF-D displayed lymph vessel invasion that extended along the bronchovascular tree beyond the main tumor. Finally, levels of VEGF-A, but not VEGF-B or VEGF-C, were higher in tumors with large nodal metastasis (> or = 1 cm) than in those with small (< 1 cm) nodal metastasis. These results support the hypothesis that two VEGF family members are involved in lymph node metastasis at two distinct steps; VEGF-C facilitates entry of cancer cells into the lymph vasculature, whereas VEGF-A promotes the growth of metastatic tumor through angiogenesis. The results also suggest

that the balance between VEGF-C and VEGF-D could be important rather than the level of VEGF-C alone. Whether a low VEGF-D level plays a causative role in lymph node metastasis requires further investigation.

L18 ANSWER 4 OF 9 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN

2001:61964 The Genuine Article (R) Number: 390XC. Vascular permeability factor/vascular endothelial growth factor (VPF/VEGF). Stiver S I (Reprint); Dvorak H F. JOURNAL OF CLINICAL LIGAND ASSAY (FAL 2000***) Vol. 23, No. 3, pp. 193-205. ISSN: 1081-1672. Publisher: CLINICAL LIGAND ASSAY SOC, 3139 S WAYNE RD, WAYNE, MI 48184 USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Current enthusiasm for the therapeutic application of angiogenesis to a wide range of disease processes derives in large part from studies of one of the most potent and biologically important growth factors, vascular permeability factor/vascular endothelial growth factor (VPF/VEGF). VPF/VEGF, also known as VEGF-A, is the foremost member of a large family of growth factors, which includes VEGF-B, VEGF-C, ***VEGF-D ,VEGF-E, and placenta growth factor (PIGF). VPF/VEGF acts as a key regulator in the angiogenic process by inducing hyperpermeability, proliferation, and migration of endothelial cells. More recently, VPF/VEGF has become recognized for its important role in promoting endothelial cell survival. The biological actions of VPF/VEGF are mediated through two tyrosine kinase receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1), selectively expressed on vascular endothelium, together with a recently discovered receptor, neuropilin. Expression of VPF/VEGF and its receptors is regulated primarily by hypoxia, other cytokines, oncogenes, and tumor suppressor genes. The signaling mechanisms of endothelial cell proliferation, migration, and hyperpermeability and the role of the anti-apoptotic AKT pathway in endothelial survival are areas of active research.

Angiogenesis mediated through VPF/VEGF is pivotal to the pathological entities of wound healing, ischemia, and tumor growth. Methods of detection and quantitation of VPF/VEGF in tissues and body fluids have become increasingly important as VPF/VEGF gains clinical importance in the diagnosis and treatment of disease.

L18 ANSWER 5 OF 9 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN

2001:116290 The Genuine Article (R) Number: 396DD. Vascular endothelial growth factor family members are differentially regulated by c-erbB signaling in head and neck squamous carcinoma cells. O-charoenrat P (Reprint); Rhys-Evans P; Modjtahedi H; Eccles S A. Inst Canc Res, McElwain Labs, Sect Canc Therapeut, Tumor Biol & Metastasis Grp, 15 Cotswold Rd, Sutton SM2 5NG, Surrey, England (Reprint); Inst Canc Res, McElwain Labs, Sect Canc Therapeut, Tumor Biol & Metastasis Grp, Sutton SM2 5NG, Surrey, England; Royal Marsden Hosp, Dept Head & Neck Surg, London SW3 6JJ, England; Univ Surrey, European Inst Hlth & Med Sci, Guildford GU2 5XH, Surrey, England. CLINICAL & EXPERIMENTAL METASTASIS (2000) Vol. 18, No. 2, pp. 155-161. ISSN: 0262-0898. Publisher: KLUWER ACADEMIC PUBL, VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Aberrant expression of tyrosine kinases such as c-erbB and EGFR contributes to the progression of head and neck squamous cell carcinomas (HNSCCs). One mechanism may be potentiation of angiogenesis, since upregulation of vascular endothelial growth factor (VEGF) expression by activation of epidermal growth factor receptor (EGFR) and/or c-erbB-2 has been described. Firstly, we demonstrated expression of all 4 members of the VEGF family in a panel of 15 HNSCC cell lines which over-express one or more c-erbB receptors. We then explored the regulatory roles of three major ligands with different selectivity of binding to c-erbB receptors

(namely transforming growth factor-alpha (TGF-alpha), betacellulin (BTC) and heregulin-beta1 (HRG-beta1)) on VEGF-A, B, C and D expression in selected HNSCC lines. Using semi-quantitative reverse transcription-PCR, we showed that all three c-erbB ligands up-regulated VEGF-A mRNA (all isoforms) and VEGF-C (BTC max at 1-10 nM; TGF-alpha and HRG-beta1 max at 10-100 nM) but had no effect on VEGF-B. Interestingly, all ligands simultaneously down-regulated the expression of VEGF-D mRNA. A monoclonal antibody (mAb) which blocks EGFR ligand binding (ICR62) down-regulated the basal levels of VEGF-A (all isoforms) and VEGF-C, had no detectable effects on VEGF-B and increased VEGF-D. ICR62 also reversed the effects of all three erbB ligands (TGF-alpha, BTC and HRG-beta1) on VEGF-A, VEGF-C and VEGF-D expression. An anti-c-erbB-2 mAb (ICR12) showed similar effects on basal or ligand-modulated expression of VEGF in these cell lines, although to a lesser extent. Our results reveal that the four VEGF genes are regulated by c-erbB signaling pathways in a strikingly different manner, suggesting that they serve distinct, although perhaps complimentary (VEGF-A and VEGF-C) or antagonistic (VEGF-D) functions. The EGFR and c-erbB-2 signaling pathway(s) plays a role in VEGF regulation in HNSCC, although EGFR would appear to be dominant in this cell type.

L18 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
2000:773478 Document No. 134:66223 Growth factors regulating lymphatic vessels. Lymboussaki, A.; Achen, M. G.; Stacker, S. A.; Alitalo, K. (Molecular/Cancer Biology Laboratory, Haartman Institute, University of Helsinki, Finland, 00014, Finland). Current Topics in Microbiology and Immunology, 251(Lymphoid Organogenesis), 75-82 (English) 2000. CODEN: CTMIA3. ISSN: 0070-217X. Publisher: Springer-Verlag.
AB A review with 44 refs. Over the past 10 yr, much has been learned about the mol. control of angiogenesis, but only recently have the first regulators of lymphangiogenesis been identified. The availability of VEGF-C and VEGF-D offers the opportunity to induce lymphangiogenesis in the clinic, which may be useful for treatment of lymphedema. The expression of VEGF-C and VEGF-D in tumors raises the possibility of tumor lymphangiogenesis. Despite involvement of the lymphatics in tumor metastasis, little is known about the relationship between tumor cells and the lymphatic endothelium. The route by which a tumor metastasizes may, in part, be determined by the angiogenic/lymphangiogenic growth factors secreted by tumor cells that modulate the prevalence of vessels in a tumor. Specific inhibitors of VEGF-C, VEGF-D or VEGFR-3 will be required to address this important issue.

L18 ANSWER 7 OF 9 MEDLINE on STN DUPLICATE 3
2001138019. PubMed ID: 11147670. Tumor angiogenesis. Detmar M. (Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown 02129, USA.. michael.detmar@cbrc2.mgh.harvard.edu) . The journal of investigative dermatology. Symposium proceedings / the Society for Investigative Dermatology, Inc. [and] European Society for Dermatological Research, (2000 Dec) Vol. 5, No. 1, pp. 20-3. Ref: 56. Journal code: 9609059. ISSN: 1087-0024. Pub. country: United States. Language: English.
AB In order to grow beyond minimal size and to metastasize, tumors need to induce the growth of new blood vessels (angiogenesis). Whereas in normal tissues, vascular quiescence is maintained by the dominant influence of endogenous angiogenesis inhibitors over angiogenic stimuli, tumor angiogenesis is induced by increased secretion of angiogenic factors and/or by downregulation of angiogenesis inhibitors. Recent evidence suggests vascular endothelial growth factor (VEGF) as the major tumor angiogenesis factor, promoting tumor growth, invasion, and metastasis. Conversely, blocking of VEGF function inhibits

angiogenesis and suppresses tumor growth in vivo. Newly identified members of the VEGF family of angiogenesis factors include placental growth factor, VEGF-B, VEGF-C, and VEGF-D, and show overlapping binding patterns to specific endothelial cell receptors. VEGF-C appears to play a major role as a lymphangiogenesis factor and as a growth factor for Kaposi's sarcoma. In contrast, endogenous inhibitors prevent blood vessel growth in normal tissues. In particular, thrombospondin-1 (TSP-1) and TSP-2 are expressed in normal skin and, when introduced into squamous cell carcinomas, potently inhibit malignant tumor growth via inhibition of tumor angiogenesis.

L18 ANSWER 8 OF 9 MEDLINE on STN DUPLICATE 4
2000017489. PubMed ID: 10551327. Expression of vascular endothelial growth factor (VEGF) family members in breast cancer. Kurebayashi J; Otsuki T; Kunisue H; Mikami Y; Tanaka K; Yamamoto S; Sonoo H. (Department of Breast & Thyroid Surgery, Kawasaki Medical School, Okayama.. kure@med.kawasaki-m.ac.jp) . Japanese journal of cancer research : Gann, (1999 Sep) Vol. 90, No. 9, pp. 977-81. Journal code: 8509412. ISSN: 0910-5050. Pub. country: Japan. Language: English.
AB Vascular endothelial growth factor (VEGF)-A is known to play an important role in tumor angiogenesis. Three additional members of the VEGF family, VEGF-B, -C and -D, have recently been discovered. VEGF-C and VEGF -D are ligands for VEGF receptor-3, which is expressed in the endothelium of lymphatic vessels. The expression of VEGF-C is known to be associated with the development of lymphatic vessels. Therefore, it is conceivable that VEGF-C and VEGF-D might play a role in the development of lymphatic vessels in solid tumors. To obtain some clue as to this role, we developed a semi-quantitative reverse transcription-polymerase chain reaction method to investigate the mRNA expression levels of each VEGF family member in breast cancer. All the VEGF family members were expressed at different levels in seven human breast cancer cell lines explored. Although VEGF-A and VEGF-B expressions were detected in both node-positive and node-negative breast tumors, VEGF-C expression was detected only in node-positive tumors. VEGF -D expression was detected only in an inflammatory breast cancer and a tumor which developed an inflammatory skin metastasis. These findings suggest a possible relationship between the expression level of VEGF-C and/or VEGF-D and the development of lymphatic tumor spread.

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2000:502196 Document No.: PREV200000487774. VEGF-C, VEGF-D and VEGFR-3 in tumor angiogenesis, lymphangiogenesis and metastasis. Alitalo, K. [Reprint author]. Molecular/Cancer Biology Laboratory, Haartman Institute, University of Helsinki, Helsinki, Finland. Clinical and Experimental Metastasis, (1999 (2000)) Vol. 17, No. 9, pp. 740. print.
Meeting Info.: VIII International Congress of the Metastasis Research Society. London, UK. September 24-27, 2000.
CODEN: CEXMD2. ISSN: 0262-0898. Language: English.

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